

**Amendments to the Claims**

1-19 (Canceled)

20. (Previously presented) A nucleic acid molecule comprising an open reading frame encoding a cleavable single-chain polypeptide, said open reading frame comprising:

- a) a first nucleotide sequence encoding at least a portion of a clostridial neurotoxin heavy chain binding element able to preferentially interact with a target cell surface marker under physiological conditions;
- b) a second nucleotide sequence encoding at least a portion of a clostridial neurotoxin heavy chain translocation element able to facilitate the transfer of said single-chain polypeptide across a vesicular membrane;
- c) a third nucleotide sequence encoding at least a portion of a therapeutic element peptide having biological activity when released into the cytoplasm of the target cell, and
- d) a fourth nucleotide sequence encoding a peptide comprising a non-native Clostridial neurotoxin protease cleavage site;

wherein said fourth nucleotide sequence intervenes between said second sequence and said third nucleotide sequence.

21. (Previously presented) The molecule of claim 20, wherein said open reading frame further comprises a fifth nucleotide sequence encoding a peptide comprising a target-binding portion of a binding tag.

22. (Previously presented) The molecule of claim 21, wherein said target-binding portion comprises a His<sub>6</sub>, a monoclonal antibody, a maltose binding protein, a glutathione-S-transferase, a protein A, or a calmodulin binding protein.

23. (Previously presented) The molecule of claim 20, wherein said binding element is a *Clostridium botulinum* neurotoxin heavy chain.

24. (Previously presented) The molecule of claim 20, wherein said translocation element is a *Clostridium botulinum* neurotoxin heavy chain.

25. (Previously presented) The molecule of claim 20, wherein said translocation element is a *Clostridium tetani* neurotoxin heavy chain.

26. (Previously presented) The molecule of claim 20, wherein said therapeutic element peptide comprises a clostridial neurotoxin light chain.

27. (Previously presented) The molecule of claim 26, wherein said clostridial neurotoxin light chain is a *Clostridium botulinum* neurotoxin light chain.

28. (Previously presented) The molecule of claim 26, wherein said clostridial neurotoxin light chain is a *Clostridium tetani* neurotoxin light chain.

29-31. (Canceled)

32. (Currently amended) A method of making a cleavable single-chain polypeptide comprising:

- a) inserting the ~~plasmid~~ nucleic acid molecule of any one of claims 20-28, 31 or 38 into a suitable host cell,
- b) growing said host cell in culture, and
- c) permitting or inducing the host cell to express the single chain polypeptide encoded by said plasmid.

33. (Currently amended) A method of purifying a cleavable single chain polypeptide comprising:

- a) lysing a host cell expressing a single chain polypeptide from the ~~plasmid~~ nucleic acid molecule of either of claim 21 or 22 to produce a cell lysate,
- b) contacting said cell lysate with a target compound so as to form a specific binding complex capable of being immobilized comprising said binding tag and said target compound, and
- c.) separating said binding complex from said cell lysate.

34-37. (Canceled)

38. (Previously presented) The molecule of claim 20, wherein said binding element is a *Clostridium tetani* neurotoxin heavy chain.

39. (Currently amended) The molecule of claim 20, wherein said protease cleavage site ~~comprising~~ comprises SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 22 or SEQ ID NO: 23.

40. (Previously presented) A nucleic acid molecule comprising an open reading frame encoding a cleavable single-chain polypeptide, said open reading frame comprising:

- a) a first nucleotide sequence encoding at least a portion of a binding element peptide able to preferentially interact with a sensory afferent neuron cell surface marker under physiological conditions;
- b) a second nucleotide sequence encoding at least a portion of a clostridial neurotoxin heavy chain translocation element able to facilitate the transfer of said single-chain polypeptide across a vesicular membrane;
- c) a third nucleotide sequence encoding at least a portion of a clostridial neurotoxin light chain therapeutic element having biological activity when released into the cytoplasm of said target cell; and
- d) a fourth nucleotide sequence encoding a peptide comprising a non-native Clostridial neurotoxin protease cleavage site;

wherein said fourth nucleotide sequence intervenes between said second sequence and said third nucleotide sequence.

41. (Previously presented) The molecule of claim 40, wherein said open reading frame further comprises a fifth nucleotide sequence encoding a peptide comprising a target-binding portion of a binding tag.
42. (Previously presented) The molecule of claim 41, wherein said target-binding portion comprises a His<sub>6</sub>, a monoclonal antibody, a maltose binding protein, a glutathione-S-transferase, a protein A or a calmodulin binding protein.
43. (Previously presented) The molecule of claim 40, wherein said translocation element is a *Clostridium botulinum* neurotoxin heavy chain.
44. (Previously presented) The molecule of claim 40, wherein said translocation element is a *Clostridium tetani* neurotoxin heavy chain.
45. (Previously presented) The molecule of claim 40, wherein said therapeutic element is a *Clostridium botulinum* neurotoxin light chain.
46. (Previously presented) The molecule of claim 40, wherein said therapeutic element is a *Clostridium tetani* neurotoxin light chain.
47. (Currently amended) The molecule of claim 40, wherein said protease cleavage site ~~comprising~~comprises SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 22 or SEQ ID NO: 23.